The whole diagram of the discovered host immunological pathways

By Wan-Chung Hu[ab]

National Research Institute of Chinese Medicine[a]
Genomics Research Center, Academia Sinica[b]

Correspondence to: Wan-Chung Hu, wanchung@nricm.edu.tw, No. 155-1 Linnong street Sec.2, Beitou district, Taipei 112, Taiwan R.O.C. 886-2-28201999ext3551

Abstract

The host immunological pathways are re-organized to get a clear picture. There are four acute immune responses: TH1/TH2/TH22/THαβ which are corresponding to four chronic immune responses: THfh/TH9/TH17/TH3. Then, the four branches of immune reactions can link to four types of hypersensitivities or allergies. Another inhibitory pathway Treg secreting TGF beta is the key player to shift the above acute immune responses to chronic immune responses for generating milder cytokines and other immune mediators to avoid severe destruction of organ during chronic and large scale of pathogen infection of tissue-organ. This 4x2+1 is the new diagram of host immunological pathways.

Overview

There are many discovered host immunological pathways including traditional TH1/TH2, TH3, TH17, TH22, THfh, Treg, TH9, and Tr1(THαβ). These identified pathways are not logically organized. Here, I will propose a detailed picture about the whole context of host immunological pathways.

Acute immunological pathways

The traditional TH1/TH2 paradigm was proposed by Dr. Mosmann in 1986.(1) TH1 was thought the host immunity against viruses and intracellular bacteria. TH2 is the host immunity against multicellular parasites (helminthes). In my PhD thesis, I proposed a new THαβ immunological pathway against viruses that is divided from

traditional TH1 immunity. The TH1 immunity is then focusing on intracellular bacteria and protozoa.

TH1 immunity is driven by IL-12. The main effector cells of TH1 immunity are macrophages, CTLs, IFNg secreting CD4 T cells, and IgG3 producing B cells. The key transcription factors for TH1 immunity is STAT4 and STAT1. T-bet also plays a vital role in TH1 immunological pathway. TH1 immunity against self antigen is Type 4 Delayed type hypersensitivity such as tuberculin BCG reaction.

TH2 immunity is driven by IL-4. The main effector cells of TH2 immunity are eosinophils, basophils, mast cells, IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells. The key transcription factor for TH2 immunity is STAT6. GATA3 also plays a vital role in TH2 immunological pathway. TH2 immunity against self antigen is Type1 IgE mediated allergy and hypersensitivity such as food allergy or urticaria.

THαβ is distinguished from the traditional TH1 immunity(2). It was called Tr1 cell by some previous researchers. THαβ immunity is driven by IFNa/b or IL-10.(3-5) The main effector cells of THαβ immunity are NK cells, IL-10/IL-27 secreting CD4 T cells, CTLs, and IgG1 producing B cells. The key transcription factor for THαβ immunity is STAT1, STAT2, and STAT3. THαβ immunity against self antigen is Type 3 Antibody dependent cellular cytotoxic hypersensitivity such as Myasthenia Gravis.

TH22 is the host innate immunity against extracellular bacteria and fungi(6, 7). TH22 is driven by IL-6 or TNFa(8, 9). The main effector cells for TH22 immunity are PMNs, IL-22 secreting CD4 T cells, complements, pentraxins, and IgM/IgG2 producing B cells.(10, 11) The key transcription factor for TH22 is STAT3(12). AP1 and CEBP are also important. TH22 against self antigen is Type 2 immune-complex and complement mediated hypersensitivity such as Arthus reaction.

Chronic immunological pathways

Treg is the host immune inhibitory mechanism(13). It is driven by IL-2 and TGF beta. The main effector cells for Treg are TGFb producing CD4 T cell and IgA producing B cell. The key transcription factor for Treg pathway is STAT5. The combination of Treg and the above four immunological pathways is important to shift acute immunity to chronic immunity. During the initial infection, acute fierce cytokines can rapidly kill pathogens as well as infected cells or tissues. However, if the pathogen infects a lot of cells in a tissue such as liver, to kill the infected cells will total destroyed the organ.

In the chronic situation, TGF beta cooperates with either IL-10(TH3), IL-6(TH17), IL-4(TH9) or IL-21(THfh) will cause B cell isotype switch to IgA.(14-17) Thus, regulatory T cells combining TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines. Then, THfh/TH9/TH17/TH3 immunological pathways will be generated in the chronic infection or hypersensitivity.

Follicular helper T cells (THfh) is thought to be the key helper cells for the B cell germinal centers. However, several key papers pointed out that it has a close relation to TH1 helper cells and THfh cells are called TH1-like cells.(18) TH1-like cells with Foxp3+ regulatory character are identified.(19, 20) IL-12 and IFNg can cause overproduction of THfh helper T cells.(21-23)IL-12 can drive the early commitment for THfh lineage and is vital to THfh development.(24-27) THfh cells are characterized by IL-21 producing T cells(28, 29). TGF beta is found to differentiate the IL-21 producing helper T cells(30-32). IL-21 production is also related to STAT4 and STAT1 activation.(33-35) But, BCL6 is key in THfh development.(36-38) In addition, STAT3(TH22) and IFNa/b(THαβ) suppress the development of THfh cells(39). And, BCL6 can suppress key TH2 transcription factor GATA3.(40) THfh or TH1-like cells are important in chronic intracellular bacterial infection or in chronic DTH autoimmune diseases(41-43). Thus, THfh or TH1-like helper T cells is the chronic T helper cells related to TH1 immnunity.(44, 45)

TH9 cell is driven by IL-4 combining TGF beta.(46) Thus, TH9 cell is closely related to TH2 immunological pathway. It is characterized by IL-9 secreting CD4 T cell. TH9 cells are found to be important in chronic allergic condition such as asthma. Thus, TH9 helper cell is the chronic T helper cells related to TH2 immunity.(47-49)

TH17 cell is driven by IL-6 / IL-1 combining TGF beta(50, 51). Thus, TH17 cell is closely related to TH22 immunological pathway. It is characterized by IL-17 secreting CD4 T cell. TH17 cells are found to be important in chronic immune-complex mediated disease such as rheumatic arthritis. Then, TH17 helper cell is the chronic T helper cell related to TH22 immunity. (52) TGF beta can suppress the acute IL-22 producing cells and enhance the chronic IL-17 producing cells(53). Because of the role of TGF beta in TH17 immunity, regulatory IL-17 producing cells are noted.(54, 55)

TH3 cells are driven by IL-10 and TGF beta.(56) Thus, TH3 cells are closely related to THαβ immunological pathway. In contrast to $CD4^{+}CD25^{+}$ Treg cells whose survival are depending on interleukin 2, the proliferation of TH3 cells rely on TGF beta and IL-10. It also produces IL-10 as well as TGF beta.(57) Thus, TH3 helper cell is important to

chronic antibody dependent cellular cytotoxic hypersensitivity. TH3 cell is the chronic helper T cells corresponding to THαβ helper cell.(58-60)

Conclusion

Thus, this eight diagram: 4x2+1 immunological pathways are the whole pictures of host immunological pathways. (Figure 1) Then, we can clearly understand the detailed immune response against acute or chronic pathogens as well as acute or chronic allergy/hypersensitivity.

Author bios

Wan-Chung Hu is a assistant research fellow (assistant professor) of National Research Institute of Chinese Medicine, Taiwan. He got his MD degree from National Taiwan University, and he received his PhD degree from Vaccine Science track, Department of International Health, Johns Hopkins University School of Public Health. Then, he was a postdoctorate of Genomics Research Center of Academia Sinica, Taiwan. In his PhD thesis, he proposed a new anti-viral THαβ immune response. Malarial infection drives host to TH17 and THαβ immunities instead of TH1 immunity for parasite survival advantage. His papers were accepted by Infection & Immunity as well as Malaria Journal. Now, his research interest is the relationship of Chinese medicine and its interaction of host immunity.

References

1. **Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL.** 1986. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. Journal of immunology (Baltimore, Md. : 1950) **136:**2348-2357.
2. **Hu WC.** 2013. Human immune responses to Plasmodium falciparum infection: molecular evidence for a suboptimal THalphabeta and TH17 bias over ideal and effective traditional TH1 immune response. Malaria journal **12:**392.
3. **Haringer B, Lozza L, Steckel B, Geginat J.** 2009. Identification and characterization of IL-10/IFN-gamma-producing effector-like T cells with regulatory function in human blood. The Journal of experimental medicine **206:**1009-1017.

4. **Kvale EO, Floisand Y, Lund-Johansen F, Rollag H, Farkas L, Ghanekar S, Brandtzaeg P, Jahnsen FL, Olweus J.** 2007. Plasmacytoid DCs regulate recall responses by rapid induction of IL-10 in memory T cells. Blood **109:**3369-3376.
5. **Levings MK, Sangregorio R, Galbiati F, Squadrone S, de Waal Malefyt R, Roncarolo MG.** 2001. IFN-alpha and IL-10 induce the differentiation of human type 1 T regulatory cells. Journal of immunology (Baltimore, Md. : 1950) **166:**5530-5539.
6. **Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK.** 2008. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nature medicine **14:**275-281.
7. **Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R.** 2004. IL-22 increases the innate immunity of tissues. Immunity **21:**241-254.
8. **Ghoreschi K, Laurence A, Yang XP, Tato CM, McGeachy MJ, Konkel JE, Ramos HL, Wei L, Davidson TS, Bouladoux N, Grainger JR, Chen Q, Kanno Y, Watford WT, Sun HW, Eberl G, Shevach EM, Belkaid Y, Cua DJ, Chen W, O'Shea JJ.** 2010. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature **467:**967-971.
9. **Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H.** 2009. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. Nature immunology **10:**864-871.
10. **Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F.** 2009. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nature immunology **10:**857-863.
11. **Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S, Cianfarani F, Odorisio T, Traidl-Hoffmann C, Behrendt H, Durham SR, Schmidt-Weber CB, Cavani A.** 2009. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. The Journal of clinical investigation **119:**3573-3585.
12. **Yoshida Y, Kumar A, Koyama Y, Peng H, Arman A, Boch JA, Auron PE.** 2004. Interleukin 1 activates STAT3/nuclear factor-kappaB cross-talk via a unique TRAF6- and p65-dependent mechanism. The Journal of biological chemistry **279:**1768-1776.
13. **Hori S, Nomura T, Sakaguchi S.** 2003. Control of regulatory T cell development by the transcription factor Foxp3. Science (New York, N.Y.)

299:1057-1061.

14. **Seo GY, Youn J, Kim PH.** 2009. IL-21 ensures TGF-beta 1-induced IgA isotype expression in mouse Peyer's patches. Journal of leukocyte biology **85:**744-750.
15. **Kunimoto DY, Ritzel M, Tsang M.** 1992. The roles of IL-4, TGF-beta and LPS in IgA switching. European cytokine network **3:**407-415.
16. **Defrance T, Vanbervliet B, Briere F, Durand I, Rousset F, Banchereau J.** 1992. Interleukin 10 and transforming growth factor beta cooperate to induce anti-CD40-activated naive human B cells to secrete immunoglobulin A. The Journal of experimental medicine **175:**671-682.
17. **Goodrich ME, McGee DW.** 1999. Preferential enhancement of B cell IgA secretion by intestinal epithelial cell-derived cytokines and interleukin-2. Immunological investigations **28:**67-75.
18. **Oestreich KJ, Mohn SE, Weinmann AS.** 2012. Molecular mechanisms that control the expression and activity of Bcl-6 in TH1 cells to regulate flexibility with a TFH-like gene profile. Nature immunology **13:**405-411.
19. **Dominguez-Villar M, Baecher-Allan CM, Hafler DA.** 2011. Identification of T helper type 1-like, Foxp3+ regulatory T cells in human autoimmune disease. Nature medicine **17:**673-675.
20. **O'Connor RA, Leech MD, Suffner J, Hammerling GJ, Anderton SM.** 2010. Myelin-reactive, TGF-beta-induced regulatory T cells can be programmed to develop Th1-like effector function but remain less proinflammatory than myelin-reactive Th1 effectors and can suppress pathogenic T cell clonal expansion in vivo. Journal of immunology (Baltimore, Md. : 1950) **185:**7235-7243.
21. **Feng T, Cao AT, Weaver CT, Elson CO, Cong Y.** 2011. Interleukin-12 converts Foxp3+ regulatory T cells to interferon-gamma-producing Foxp3+ T cells that inhibit colitis. Gastroenterology **140:**2031-2043.
22. **Lee SK, Silva DG, Martin JL, Pratama A, Hu X, Chang PP, Walters G, Vinuesa CG.** 2012. Interferon-gamma excess leads to pathogenic accumulation of follicular helper T cells and germinal centers. Immunity **37:**880-892.
23. **Zheng J, Liu Y, Qin G, Lam KT, Guan J, Xiang Z, Lewis DB, Lau YL, Tu W.** 2011. Generation of human Th1-like regulatory CD4+ T cells by an intrinsic IFN-gamma- and T-bet-dependent pathway. European journal of immunology **41:**128-139.
24. **Ma CS, Suryani S, Avery DT, Chan A, Nanan R, Santner-Nanan B, Deenick EK, Tangye SG.** 2009. Early commitment of naive human CD4(+) T cells to the T follicular helper (T(FH)) cell lineage is induced by IL-12. Immunology and cell

biology **87:**590-600.

25. **Prochazkova J, Pokorna K, Holan V.** 2012. IL-12 inhibits the TGF-beta-dependent T cell developmental programs and skews the TGF-beta-induced differentiation into a Th1-like direction. Immunobiology **217:**74-82.
26. **Schmitt N, Bustamante J, Bourdery L, Bentebibel SE, Boisson-Dupuis S, Hamlin F, Tran MV, Blankenship D, Pascual V, Savino DA, Banchereau J, Casanova JL, Ueno H.** 2013. IL-12 receptor beta1 deficiency alters in vivo T follicular helper cell response in humans. Blood **121:**3375-3385.
27. **Schmitt N, Morita R, Bourdery L, Bentebibel SE, Zurawski SM, Banchereau J, Ueno H.** 2009. Human dendritic cells induce the differentiation of interleukin-21-producing T follicular helper-like cells through interleukin-12. Immunity **31:**158-169.
28. **Fina D, Sarra M, Caruso R, Del Vecchio Blanco G, Pallone F, MacDonald TT, Monteleone G.** 2008. Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease. Gut **57:**887-892.
29. **Luthje K, Kallies A, Shimohakamada Y, Belz GT, Light A, Tarlinton DM, Nutt SL.** 2012. The development and fate of follicular helper T cells defined by an IL-21 reporter mouse. Nature immunology **13:**491-498.
30. **Liu Y, Yu S, Li Z, Ma J, Zhang Y, Wang H, Yang B, Wu C.** 2013. TGF-beta enhanced IL-21-induced differentiation of human IL-21-producing CD4+ T cells via Smad3. PloS one **8:**e64612.
31. **Marshall HD, Ray JP, Laidlaw BJ, Zhang N, Gawande D, Staron MM, Craft J, Kaech SM.** 2015. The transforming growth factor beta signaling pathway is critical for the formation of CD4 T follicular helper cells and isotype-switched antibody responses in the lung mucosa. eLife **4:**e04851.
32. **Schmitt N, Liu Y, Bentebibel SE, Munagala I, Bourdery L.** 2014. The cytokine TGF-beta co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells. **15:**856-865.
33. **Agrawal A, Su H, Chen J, Osann K, Agrawal S, Gupta S.** 2012. Increased IL-21 secretion by aged CD4+T cells is associated with prolonged STAT-4 activation and CMV seropositivity. Aging **4:**648-659.
34. **Choi YS, Eto D, Yang JA, Lao C, Crotty S.** 2013. Cutting edge: STAT1 is required for IL-6-mediated Bcl6 induction for early follicular helper cell differentiation. Journal of immunology (Baltimore, Md. : 1950) **190:**3049-3053.
35. **Strengell M, Sareneva T, Foster D, Julkunen I, Matikainen S.** 2002. IL-21 up-regulates the expression of genes associated with innate immunity and Th1 response. Journal of immunology (Baltimore, Md. : 1950) **169:**3600-3605.
36. **Baumjohann D, Okada T, Ansel KM.** 2011. Cutting Edge: Distinct waves of

BCL6 expression during T follicular helper cell development. Journal of immunology (Baltimore, Md. : 1950) **187:**2089-2092.

37. **Linterman MA, Beaton L, Yu D, Ramiscal RR, Srivastava M, Hogan JJ, Verma NK, Smyth MJ, Rigby RJ, Vinuesa CG.** 2010. IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. The Journal of experimental medicine **207:**353-363.
38. **Nurieva RI, Chung Y, Martinez GJ, Yang XO, Tanaka S, Matskevitch TD, Wang YH, Dong C.** 2009. Bcl6 mediates the development of T follicular helper cells. Science (New York, N.Y.) **325:**1001-1005.
39. **Ray JP, Marshall HD, Laidlaw BJ, Staron MM, Kaech SM, Craft J.** 2014. Transcription factor STAT3 and type I interferons are corepressive insulators for differentiation of follicular helper and T helper 1 cells. Immunity **40:**367-377.
40. **Sawant DV, Sehra S, Nguyen ET, Jadhav R, Englert K, Shinnakasu R, Hangoc G, Broxmeyer HE, Nakayama T, Perumal NB, Kaplan MH, Dent AL.** 2012. Bcl6 controls the Th2 inflammatory activity of regulatory T cells by repressing Gata3 function. Journal of immunology (Baltimore, Md. : 1950) **189:**4759-4769.
41. **Ko HJ, Yang H, Yang JY, Seo SU, Chang SY, Seong JK, Kweon MN.** 2012. Expansion of Tfh-like cells during chronic Salmonella exposure mediates the generation of autoimmune hypergammaglobulinemia in MyD88-deficient mice. European journal of immunology **42:**618-628.
42. **Monteleone G, Monteleone I, Fina D, Vavassori P, Del Vecchio Blanco G, Caruso R, Tersigni R, Alessandroni L, Biancone L, Naccari GC, MacDonald TT, Pallone F.** 2005. Interleukin-21 enhances T-helper cell type I signaling and interferon-gamma production in Crohn's disease. Gastroenterology **128:**687-694.
43. **Ulrichs T, Kosmiadi GA, Trusov V, Jorg S, Pradl L, Titukhina M, Mishenko V, Gushina N, Kaufmann SH.** 2004. Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. The Journal of pathology **204:**217-228.
44. **Duan M, Huang Y, Zhong X, Tang H.** 2014. IL-21 is increased in peripheral blood of emphysema mice and promotes Th1/Tc1 cell generation in vitro. Inflammation **37:**745-755.
45. **Nakayamada S, Kanno Y, Takahashi H, Jankovic D, Lu KT, Johnson TA, Sun HW, Vahedi G, Hakim O, Handon R, Schwartzberg PL, Hager GL, O'Shea JJ.** 2011. Early Th1 cell differentiation is marked by a Tfh cell-like transition. Immunity **35:**919-931.

46. **Dardalhon V, Awasthi A, Kwon H, Galileos G, Gao W, Sobel RA, Mitsdoerffer M, Strom TB, Elyaman W, Ho IC, Khoury S, Oukka M, Kuchroo VK.** 2008. IL-4 inhibits TGF-beta-induced Foxp3+ T cells and, together with TGF-beta, generates IL-9+ IL-10+ Foxp3(-) effector T cells. Nature immunology **9:**1347-1355.
47. **Veldhoen M, Uyttenhove C, van Snick J, Helmby H, Westendorf A, Buer J, Martin B, Wilhelm C, Stockinger B.** 2008. Transforming growth factor-beta 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset. Nature immunology **9:**1341-1346.
48. **Putheti P, Awasthi A, Popoola J, Gao W, Strom TB.** 2010. Human CD4 memory T cells can become CD4+IL-9+ T cells. PloS one **5:**e8706.
49. **Soroosh P, Doherty TA.** 2009. Th9 and allergic disease. Immunology **127:**450-458.
50. **Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, Ma L, Watowich SS, Jetten AM, Tian Q, Dong C.** 2009. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity **30:**576-587.
51. **Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT.** 2005. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nature immunology **6:**1123-1132.
52. **Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA.** 2006. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. The Journal of experimental medicine **203:**2271-2279.
53. **Rutz S, Noubade R, Eidenschenk C, Ota N, Zeng W, Zheng Y, Hackney J, Ding J, Singh H, Ouyang W.** 2011. Transcription factor c-Maf mediates the TGF-beta-dependent suppression of IL-22 production in T(H)17 cells. Nature immunology **12:**1238-1245.
54. **Beriou G, Costantino CM, Ashley CW, Yang L, Kuchroo VK, Baecher-Allan C, Hafler DA.** 2009. IL-17-producing human peripheral regulatory T cells retain suppressive function. Blood **113:**4240-4249.
55. **Voo KS, Wang YH, Santori FR, Boggiano C, Wang YH, Arima K, Bover L, Hanabuchi S, Khalili J, Marinova E, Zheng B, Littman DR, Liu YJ.** 2009. Identification of IL-17-producing FOXP3+ regulatory T cells in humans. Proceedings of the National Academy of Sciences of the United States of America **106:**4793-4798.
56. **Chen ZM, O'Shaughnessy MJ, Gramaglia I, Panoskaltsis-Mortari A, Murphy WJ, Narula S, Roncarolo MG, Blazar BR.** 2003. IL-10 and TGF-beta induce

alloreactive CD4+CD25- T cells to acquire regulatory cell function. Blood **101:**5076-5083.

57. **O'Garra A, Vieira PL, Vieira P, Goldfeld AE.** 2004. IL-10-producing and naturally occurring CD4+ Tregs: limiting collateral damage. The Journal of clinical investigation **114:**1372-1378.
58. **Weiner HL.** 2001. Oral tolerance: immune mechanisms and the generation of Th3-type TGF-beta-secreting regulatory cells. Microbes and infection / Institut Pasteur **3:**947-954.
59. **Weiner HL.** 2001. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. Immunological reviews **182:**207-214.
60. **Doetze A, Satoguina J, Burchard G, Rau T, Loliger C, Fleischer B, Hoerauf A.** 2000. Antigen-specific cellular hyporesponsiveness in a chronic human helminth infection is mediated by T(h)3/T(r)1-type cytokines IL-10 and transforming growth factor-beta but not by a T(h)1 to T(h)2 shift. International immunology **12:**623-630.

Figure 1: The whole immunological pathway diagram

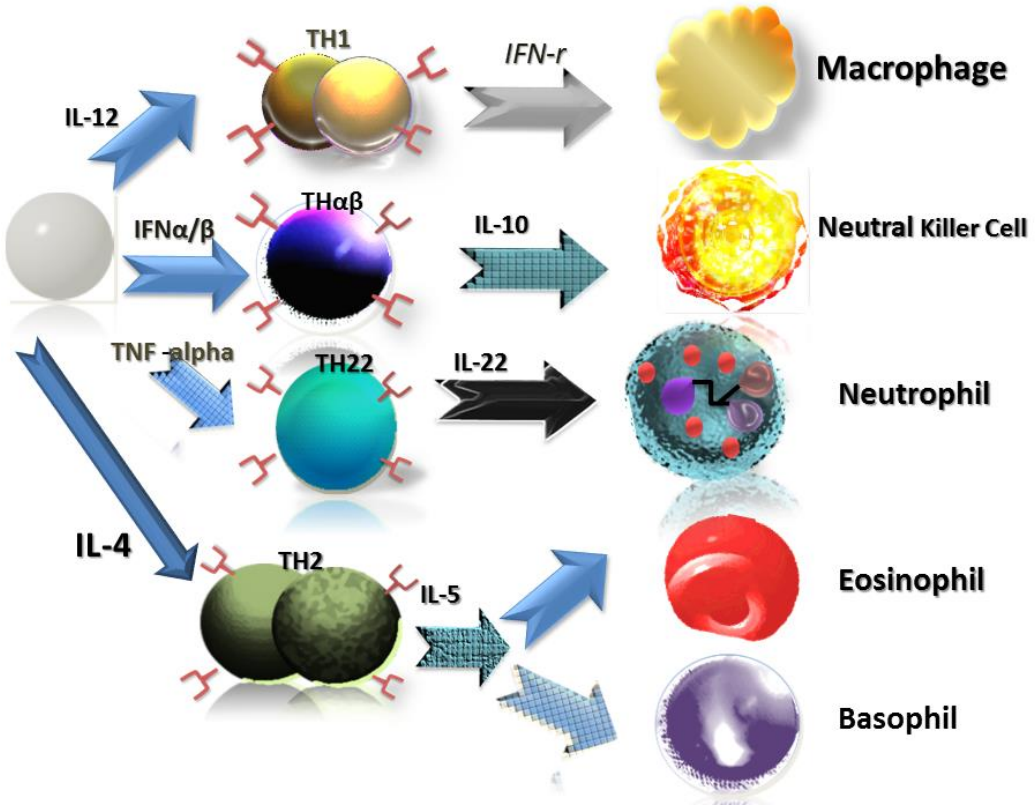

Figure 2: Acute host immunological pathways

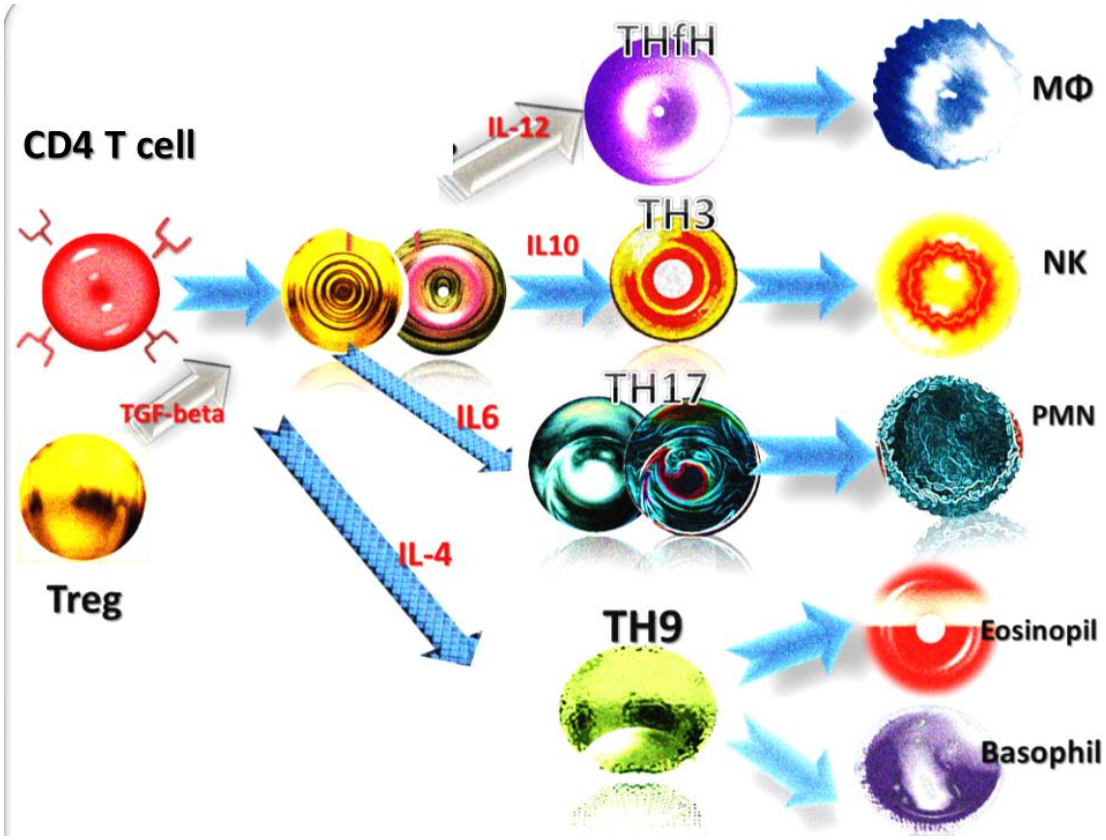

Figure 3: Chronic host immunological pathways